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Antagonists	Argos	Melanogaster	Drosophila
Agonists			
Lin-3			
Vein	PGYRLFAGGSP-LTRLCEORKOPQKLFTVRKQEFVLDEVNINSLGPK--GHRCEPSHHTQSG-		
Gurken			
Spitz			
Keren			
NRG1_alpha			
NRG1_beta			
NRG2_alpha			
NRG2_beta			
NRG3			
NRG4			
EGF			
TGF_alpha			
Beta-cellulin			
Amphiregulin			
HB-EGF			
Epiregulin			
Epigen			
Agonists			
Lin-3			
I EKLKEAKQKD-----YGHNNATEHVEVIFRED---RVSAVVPSPHGPQGWRGTRGDRHYVQAF-			
Vein	DRSASGIPQN--FD--YGFHNGTQRMIPDIN-----EVY--GRCPTEXFGNRCENKWPDSR-	D. Melanogasta	
Gurken	ETEIQMLPQSEAYNTSFQNLGGHCFQHPMVNN-----TVEFHSGLQWNDYGERCAYKSWNGD-	D. Melanogasta	
Spitz	NITFPTYKCPPETDWYQINDAHGFAVKIADL-----PVYS-GECAITGENGQRCYEKEIDNT-	D. Melanogasta	
Keren	NVTFPFAGGPPPTVWYQBLNDGTGFTVKHNE-----ILYN-CEGLGNGPGRCEYEKEIDGS-	D. Melanogasta	
NRG1_alpha	TGTSHLUVKQAEKEKT-PFVNGGEQFMVKDLS-----NPSRYLQKQPGFTGARCFENVPMKV-	Homo sapiens	
NRG1_beta	TGTSHLUVKQAEKEKT-PFVNGGEQFMVKDLS-----NPSRYLQKQPGFTGQDQGKQVNYMASF-	Homo sapiens	
NRG2_alpha	SWSGHARKQNETAKS-YVNGGGVQYYIEGIN-----QLS-----CKOPNGFEGQRQCLEKLPLRL-	Homo sapiens	
NRG2_beta	SWSGHARKQNETAKS-YVNGGGVQYYIEGIN-----QLS-----OKOPVGYTGDKQGQFAMVN-	Homo sapiens	
NRG3	ERSEHFKPQDRDKOLA-YGLNDGECHFVIETLTG-----SHK-----HORQREGYQGVRCDDQ-FLPKTD	Homo sapiens	
NRG4	MPTDHEEPCGGPSHKS-FQCLNGGGVYIPTIP-----SP---FCRGAVENTGARQEEVFLPGS-	Homo sapiens	
EGF	SVRNSDSECPPLSHDG-YCLHDGVQMYIEALD-----KYA-----GNCWVGYTGERCDYRDLKWW-	Homo sapiens	
TGF_alpha	AVVSHFNDCPDSHTQ-FQTH-GTCRFLVQED-----KPA-----GVCCHSGVYGARCEHADLLAV-	Homo sapiens	
Beta-cellulin	KRKGHFSRQPKQYKH-YIK-GRGRFTVVAEQ-----TPS-----GCVGDECYTGARCEVRLFLYI-	Homo sapiens	
Amphiregulin	RNRKKKNPQNAEFQN-FQIH-GECKYIEHL-----AVT-----GCKQOQEYGERCEKSMKTH-	Homo sapiens	
HB-EGF	GLGKKRDPQLRKYKD-FQIH-GECKYVKELR-----APS-----GCHLPGYHGERCHGLSLPVE-	Homo sapiens	
Epiregulin	VAQVSITKQSSDMNG-YQHL-GQCIYLVDM-----QNY-----GRCHEVGTGARCEHFFLTVH-	Homo sapiens	
Epigen	VALKFSHPQLEDHNS-YQIN-GACQAFHHELK-----QAI-----GRCFTGYTGERCEHLLTTSY-	Mus musculus	
Conserved cysteine #:	1	2	3

Figure 1

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Figure 2

Figure 3

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HUMAN	Exon A ----->	Exon B ----->	Sequence ID #
NRG1_alpha	ITGTSHLIVKCAEKEKTKCNGGCFMVKDLSNPSRYLCKCOPGFTGARCTENVPMKVQ...	14	
NRG1_beta	ITGTSHLIVKCAEKEKTKCNGGCFMVKDLSNPSRYLCKCNEFTGDRCONYVMASFY...	15	
Translated genomic locus	ITGTSHLIVKCAEKEKTKCNGGCFMVKDLSNPSRYLCK*	73, 128	
NRG2_alpha	ISWSGHARKNETAKSYCIVNGCIVIEGINOLSTCKCPNGFFGQRCLEKLPLRLY...	16	
NRG2_beta	ISWSGHARKNETAKSYCIVNGCIVIEGINOLSTCKCPVGYTGDRCQQFAMVNFY...	17	
Translated genomic locus	ISWSGHARKNETAKSYCIVNGCIVIEGINOLSTCK*	74, 129	
NRG3	ERSEHEFKPCRDKDLYCLNDGECEVYETITGSH-EKHCRCKEYGQGVRCQ-FLPKTD...	18	
Translated genomic locus	ERSEHEFKPCRDKDLYCLNDGECEVYETITGSH-EKHCR*	75, 130	
NRG4	MPTDHEEPCGSPSHKSFCIENGGLCYVITPTIPSPF-CRQEVENYGTARCEEVFLPGSS...	19	
Translated genomic locus	MPTDHEEPCGSPSHKSFCIENGGLCYVITPTIPSPF-CR*	76, 131	
EGF	SVRNSDSECPISHDGYCLHDGVCMIEALDKVA--CNGIVGYIGER-COYRDLKWE...	20	
Translated genomic locus	SVRNSDSECPISHDGYCLHDGVCMIEALDKVA--CNGIVGYIGER-COYRDLKWE*	77, 132	
TGF_alpha	AVVSHENDCPDSHTOFCEH-TGICRFIVQEDKPA-CVCHSGYYGARCEHADLLAVV...	21	
Translated genomic locus	AVVSHENDCPDSHTOFCEH-TGICRFIVQEDKPA-CV*	78, 133	
Betaacellulin	IKRKKGHESRCPKOYKHYCIK-GRCREVVAEOTPS-CVCDEGYIGARCEVLDLYR...	22	
Translated genomic locus	IKRKKGHESRCPKOYKHYCIK-GRCREVVAEOTPS-CVC*	79, 134	

Figure 4

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Amphiregulin Translated genomic locus	RNRKKKNP[NAEFQNF]I[...] RNRKKKNP[NAEFQNF]I[...]	CK[QOEYFGER]GEKSMKTHS... CK[QOEYFGER]GEKSMKTHS...	23 80, 135
HB-EGF Translated genomic locus	GLGKKRDP[GLRKYKDF]I[...] GLGKKRDP[GLRKYKDF]I[...]	C[IC]HPGYHGER[CHG]LSPV[...] C[IC]HPGYHGER[CHG]LSPV[...]	24 81, 136
Epiregulin Translated genomic locus	VAQSVITK[SSD]NG[...] VAQSVITK[SSD]NG[...]	[C]T[GOC]YLVDMSONY[...] [C]T[GOC]YLVDMSONY[...]	25 82, 137
Epigen(Mouse) Trans. mouse genomic locus Trans. human genomic locus	VALKFSHPC[EDHNS]C[...] VALKFSHPC[EDHNS]C[...] VALKFSHLC[EDHNS]C[...]	[C]T[GAC]FH[EL]KOA[...] [C]T[GAC]FH[EL]KOA[...] [C]T[GAC]FH[EL]KOA[...]	26 83, 84, 138 84, 139

Figure 4 (continued)

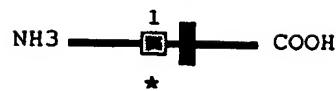
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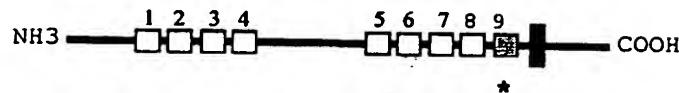
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i) TGF-alpha



ii) Epidermal Growth Factor



iii) Notch 1

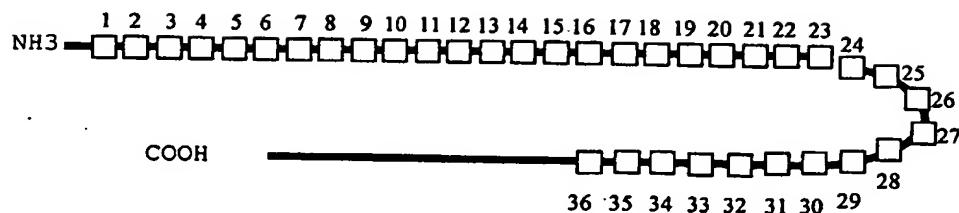


Figure 5A

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i) TGF alpha
 EGF DOMAIN NUMBER
 1. EGF_47_82 * Sequence ID #
 QPPSKLLOQCE-HGT-CREWQEDKPAQVCHSG--YVGAR--C 72

ii) EPIDERMAL GROWTH FACTOR
 EGF DOMAIN NUMBER
 1. EGF_318_354 Sequence ID #
 CKTR-KGNGS--STVGGCDP--QSHLCMGAEGYALSRDRKYG 27
 2. EGF_360_395 GATL-NVCC--TIEGCKQTP--CSVACICPVGWLTIPDGKTC 28
 3. EGF_401_436 GPRN-VSEC--SHDCVITS--EGPCTCAGREGSVMERDGKTC 29
 4. EGF_439_476 GSSPDLNGCCS--TOLCVPLSP--VSWECDCEPGCDLQDDEKSG 30
 5. EGF_745_780 QDYO-NGCC--TCHGCKQTP--GIANGSCREGEMLVASDGKTC 31
 6. EGF_835_868 GPRV--GGS-YKAGTISDC--EDAVTCGCGIKG--DYGDGKTC 32
 7. EGF_874_910 GEMC--VPVGCPPASVKCENIIS--CCAVCRGSIG--YQGDCPHG 33
 8. EGF_916_951 GOLC-VISCCENAS-CIATP--CCVSGICACR--LSEPGCILC 34
 9. EGF_976_1012 * QETSHDG-CI-HDGCVQVMDTALDRQZACNCVVG--YIGER--C 35

iii) Notch1 Sequence ID #

EGF DOMAIN NUMBER
 1. EGF_24_57 Sequence ID #
 CSQ-----PGETCLNGGKCEAANGTE---ACVCG-GAFVGPRC 36
 2. EGF_63_98 GKS-----TPCKNAGTCI--VADRRGVADYAGSCA--EGESGPIG 37
 3. EGF_106_138 CTT-----NPCCRNGGICD--LILTHI--EYKGRCP--PGWSGKSC 38
 4. EGF_144_175 CAS-----NPCCANGGOC--IPIEEASYIQCOP--PSHGPNG 39
 5. EGF_182_215 CGO-----KPRIICRHGGTCHNEVGSY--RCVCR-ATHTGPN 40
 6. EGF_222_254 GSPSP-----CONGGTCRPTGDV--THECAGL--PGFTGQNC 41
 7. EGF_261_292 CGCANN-----CKNCCGACV--DCVNT--TNGPGP--PEWTCOYC 42
 8. EGF_299_332 COL-----MPNAQNGGTCGHNTHGYY--NCVGV-NGWTCEDG 43
 9. EGF_339_370 CAS-----AACCHGATCH-DRVA--SEYCECP--HGRTGLLC 44
 10. EGF_376_409 CTS-----NPCCNEGSNCD-TNEPV--NGKAIGTCP--SGYTGPAQ 45
 11. EGF_416_449 CSL-----CANPCEHAGKCINTLGSF---ECQCL-QGYTGPRC 46
 12. EGF_456_487 CVS-----NPCCNDATGCF-DOIG--EFOCMCM--PGYEGVHC 47
 13. EGF_494_525 CAS-----SPCCHNGRCL-DKIN--EFOCECP--TGFTHGLC 48
 14. EGF_532_563 GAS-----TPCKNAGKCL-DCPN--TXYCVCT--EGYTGTTHC 49
 15. EGF_570_600 GDPDF-----CHYC-SCK-DCVAT--TTFGICR--PGYTGHHG 50
 16. EGF_607_638 GSS-----OPCRIRGTCQ--DPPN--AYLCHOL-KCUTGPN 51
 17. EGF_645_675 CAS-----SPC-DSGTCI--DKID--GECACE--PGYTGSMC 52
 18. EGF_682_713 GAG-----NPCHNCGIC--ED-GINGETCRCP--EGVHDPTG 53
 19. EGF_720_750 GNS-----NECVHGAIRD--SLN--GKCDCD--PGWSGTNC 54
 20. EGF_757_788 GCS-----NPCVNGGTC--D-MTS--GIVCTCR--EGESG PNC 55
 21. EGF_795_826 GAG-----NPCLINKGIC--TDD--VAGKCNCL-IPYTGATC 56
 22. EGF_833_867 GPR-----SPCRNGGCR-QSED-YES-ESCVGETAGAKGQTC 57
 23. EGF_874_905 GVL-----SPCRHGASCO-NTHC--XYRCHCO-AGYSGRN 58
 24. EGF_912_943 GPNP-----CHNGGSCT-DGIN---TAFCDCL-PGFRGTFC 59
 25. EGF_950_981 GAS-DP-----CRNGANCI-DCVD--SWKGTCP-ACESGIHC 60
 26. EGF_988_1019 GTESS-----CFNNGGTCV-DGIN---SFTCLCP-PGFTGSYC 61
 27. EGF_1026_1057 GDS-----RPTCLNGGTC-DC--RGIHRCTCP--QCYTCPNG 62
 28. EGF_1064_1095 GDS-----SPCKNNGKCN-QT--HTQYRCECP--SGWTGTYC 63
 29. EGF_1102_1143 GPPVVAQRCGVDVARLQHGLCV-DAGN---THHCRGQ-AGYTGSYC 64
 30. EGF_1150_1181 GSP-----SPCNGANCI--DYIC--GYSCKCV-AGYHGVNC 65
 31. EGF_1188_1219 GUS-----HPCCONCGTOL-DLPN--TMKCSGP-RGTOGVHC 66
 32. EGF_1226_1265 GNPVWDPVSRSP--PKCFNNGTCV-DOVG--GYSCTCP-PGEVGERG 67
 33. EGF_1272_1305 GTS-----NPCCDARGTQN-CVOR--VNDEHCECR-ACHTERRC 68
 34. EGF_1312_1346 GKC-----TPCKNCGCTA-VASN-TARGTICKCP-AGFEGATC 69
 35. EGF_1353_1384 G-----GSLRCLNGGTCISGPRSP--TOLCP-GPFTGPEG 70
 36. EGF_1392_1426 G-----GGNPCTYNOGTCEPTSESPE--YRCLCP-AKENGHLC 71

Figure 5B

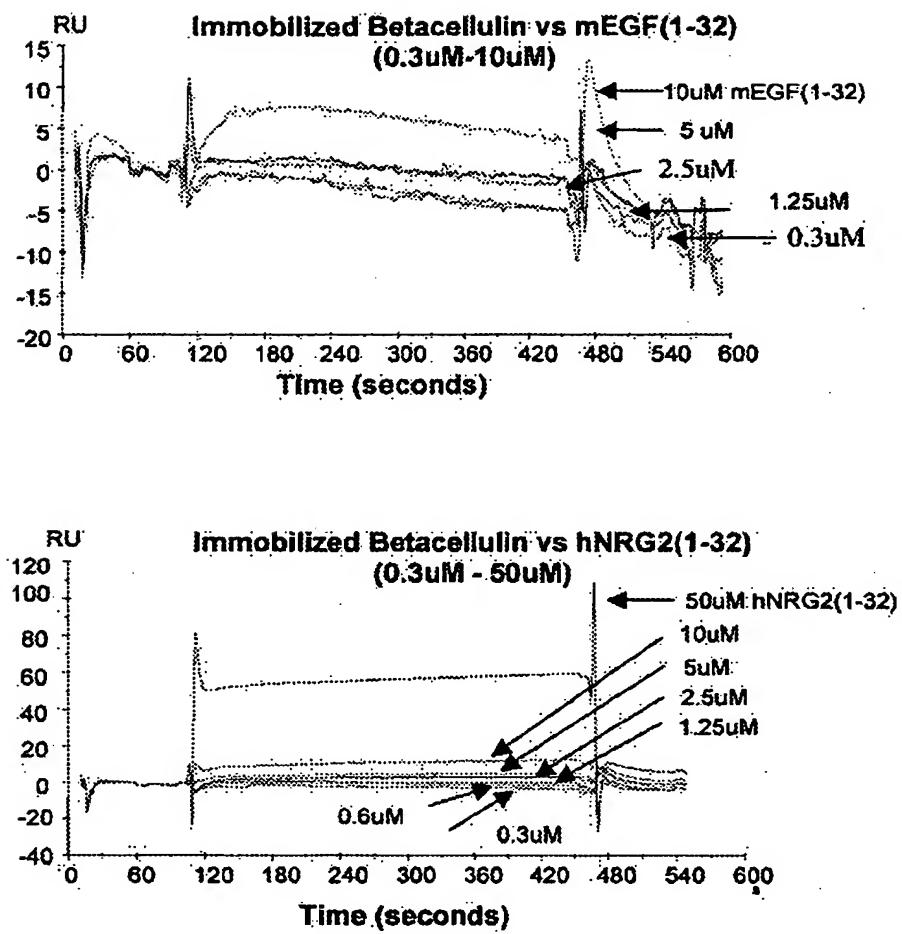


Figure 6